Angiopoietin-2: An Attractive Target for Improved Antiangiogenic Tumor Therapy
Damien Gerald, Sudhakar Chintharlapalli, Hellmut G. Augustin, and Laura E. Benjamin

Clonidine Précis: Clonidine is a widely used α2-adrenergic agonist that has been shown to have antinociceptive effects in animal models.

Chlorpromazine Précis: Chlorpromazine is a phenothiazine antipsychotic that has been shown to have antinociceptive effects in animal models.

Dexmedetomidine Précis: Dexmedetomidine is a selective α2-adrenergic agonist that has been shown to have antinociceptive effects in animal models.

Fentanyl Précis: Fentanyl is a synthetic opioid analgesic that has been shown to have antinociceptive effects in animal models.

Hypnosis Précis: Hypnosis is a state of heightened suggestibility that has been shown to have antinociceptive effects in animal models.

Methadone Précis: Methadone is a synthetic opioid analgesic that has been shown to have antinociceptive effects in animal models.

Opioid Précis: Opioids are a class of drugs that have been shown to have antinociceptive effects in animal models.

Perazosin Précis: Perazosin is a selective α1-adrenergic antagonist that has been shown to have antinociceptive effects in animal models.

Propofol Précis: Propofol is a short-acting intravenous anesthetic that has been shown to have antinociceptive effects in animal models.

Ranitidine Précis: Ranitidine is a histamine H2 receptor antagonist that has been shown to have antinociceptive effects in animal models.

Remifentanil Précis: Remifentanil is a short-acting intravenous opioid that has been shown to have antinociceptive effects in animal models.

Tramadol Précis: Tramadol is a centrally acting opioid analgesic that has been shown to have antinociceptive effects in animal models.
LOX-Mediated Collagen Crosslinking Is Responsible for Fibrosis-Enhanced Metastasis

Thomas R. Cox, Demelza Bird, Ann-Marie Baker, Holly E. Barker, Melissa W-Y. Ho, Georgina Lang, and Janine T. Erler

Précis: The fibrotic status of a metastatic niche that is determined by the extracellular matrix plays a pivotal role in determining colonization of new sites by circulating tumor cells.

Evidence for a Role of the PD-1:PD-L1 Pathway in Immune Resistance of HPV-Associated Head and Neck Squamous Cell Carcinoma


Précis: HPV-associated oropharyngeal cancers, which are increasing in incidence in the developed world, evade immune surveillance through an escape pathway that is actively being targeted in clinical trials.

IFN-γ-Mediated Downregulation of LXA4 Is Necessary for the Maintenance of Nonresolving Inflammation and Papilloma Persistence

Chunhui Wang, Mingjie Xiao, Xiaoman Liu, Chen Ni, Jianhong Liu, Ulrike Erben, and Zhihai Qin

Précis: By helping resolve an inflammatory response, IFNγ blockade can promote tumor regression by reprogramming the inflammatory microenvironment.

Myeloid-Specific Expression of Ron Receptor Kinase Promotes Prostate Tumor Growth

Devika Gurusamy, Jerilyn K. Gray, Peterson Pathrose, Rishikesh M. Kulkarni, Fred D. Finkleman, and Susan E. Waltz

Précis: This study suggests a new strategy to treat prostate tumors, by blocking a tyrosine kinase that supports tumor-associated macrophages that drive immune escape.

HLA-Restricted CTL That Are Specific for the Immune Checkpoint Ligand PD-L1 Occur with High Frequency in Cancer Patients

Shamaila Munir, Gitte Holmen Andersen, Özcan Met, Marco Donia, Thomas Mørch Frøsig, Stine Kiaer Larsen, Tobias Wiernfeldt Klausen, Inge Marie Svane, and Mads Hald Andersen

Précis: PD-L1-specific cytotoxic T cells described for the first time in this study may be useful to harness for cancer immunotherapy to defeat mechanisms of immune escape used in various cancers mediated by the PD1 pathway.

A Chimeric Receptor with NKG2D Specificity Enhances Natural Killer Cell Activation and Killing of Tumor Cells

Yu-Hsiang Chang, John Connolly, Noriko Shimasaki, Kousaku Mimura, Koji Kono, and Dario Campana

Précis: Findings illustrate how to increase the antitumor efficacy of NK cell therapy, a strategy that may be used to fight nearly any kind of human cancer.

Transcription Factor YY1 Contributes to Tumor Growth by Stabilizing Hypoxia Factor HIF-1α in a p53-Independent Manner

Shourong Wu, Vivi Kasim, Mitsunobu R. Kano, Sayaka Tanaka, Shinsuke Ohba, Kanjiro Miyata, Xueying Liu, Ako Matsushashi, Ung-il Chung, Li Yang, Kazunori Katoaka, Nobuhiro Nishiyama, and Makoto Miyagishi

Précis: Findings suggest a mechanistic strategy to block a core hypoxia-driven progression pathway regardless of p53 status.

Arkadia Regulates Tumor Metastasis by Modulation of the TGF-β Pathway

Marco A. Briones-Orta, Laurence Levy, Chris D. Madsen, Debipriya Das, Yigit Erker, Erik Sahai, and Caroline S. Hill

Précis: An E3 ubiquitin ligase in the TGF-β signaling pathway is not required to regulate tumor growth but to colonize metastasis sites, suggesting novel antimetastatic strategies.

Phosphorylation of Ribosomal Protein S6 Attenuates DNA Damage and Tumor Suppression during Development of Pancreatic Cancer

Abed Khalaileh, Avigail Dreazen, Areej Khatib, Roy Apel, Avital Swisa, Norma Kidess-Bassir, Anirban Maitra, Oded Meyuhas, Yuval Dor, and Gideon Zamir

Précis: Findings reveal that a key mTOR effector molecule is crucial for initiation of K-Ras-driven pancreatic cancers, illuminating the centrality of this mTOR pathway to evade p53-mediated tumor suppression in this setting.
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<td>1831</td>
<td>Proliferation-Independent Control of Tumor Glycolysis by PDGFR-Mediated AKT Activation</td>
<td>Cong Ran, Huan Liu, Yasuyuki Hitoshi, and Mark A. Israel</td>
<td>Precise: Findings argue that tyrosine kinase growth factor signaling directly affects glucose metabolism in glioma and is not a secondary response to enhanced proliferation, as suggested in other cancer models.</td>
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<td>1844</td>
<td>Telomere Length and Telomerase Activity Impact the UV Sensitivity Syndrome Xeroderma Pigmentosum C</td>
<td>Gerdine J. Stout and Maria A. Blasco</td>
<td>Precise: Findings reveal a role for the DNA repair protein XPC in telomere stability and how activation occurs for the ALT pathway of telomere maintenance, a broadly important aspect of tumor formation.</td>
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<td>1855</td>
<td>xCT Inhibition Depletes CD44v-Expressing Tumor Cells That Are Resistant to EGFR-Targeted Therapy in Head and Neck Squamous Cell Carcinoma</td>
<td>Momoko Yoshikawa, Kenji Tsuchihashi, Takatsugu Ishimoto, Toshifumi Yae, Takeshi Motohara, Eiji Suqihara, Nobuyuki Onishi, Takashi Masuko, Kunio Yoshizawa, Shuichi Kawashiri, Makio Mukai, Seiji Asoda, Hiromasa Kawana, Taneaki Nakagawa, Hideyuki Saya, and Osamu Nagano</td>
<td>Precise: Cells that express variant isoforms of the stem cell-determining factor CD44 rely on the activity of a cystine transporter subunit that affects redox status and EGFR function.</td>
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<td>1867</td>
<td>MicroRNA-Related Genetic Variants Associated with Clinical Outcomes in Early-Stage Non–Small Cell Lung Cancer Patients</td>
<td>Xia Pu, Jack A. Roth, Michelle A.T. Hildebrandt, Yuanying Ye, Hua Wei, John D. Minna, Scott M. Lippman, and Xifeng Wu</td>
<td>Precise: This large study of non-small cell lung cancer suggests that miRNA-related polymorphisms can predict clinical outcomes at a level that may be superior to other markers developed previously.</td>
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<td>1876</td>
<td>Genetic Variation in Transforming Growth Factor Beta 1 and Mammographic Density in Singapore Chinese Women</td>
<td>Eunjung Lee, David Van den Berg, Chris Hsu, Giske Ursin, Woon-Puay Koh, Jian-Min Yuan, Daniel O. Stram, Mimi C. Yu, and Anna H. Wu</td>
<td>Precise: Host genetic polymorphisms in a key growth factor in breast cancer may help identify women at an increased risk of breast cancer.</td>
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<td>1883</td>
<td>Identification of Inherited Genetic Variations Influencing Prognosis in Early-Onset Breast Cancer</td>
<td>Sajjad Rafiq, William Tapper, Andrew Collins, Sofia Khan, Ioannis Politopoulos, Sue Gerty, Carl Blomqvist, Fergus J. Couch, Helgi Nevanlinna, Tianjun Liu, and Diana Eccles</td>
<td>Precise: This study maps host genetic variations that affect risks of poor prognosis in early onset breast cancer patients, with implications for how aggressive treatments should be used to improve survival outcomes.</td>
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<td>1892</td>
<td>Focused Ultrasound Delivers Targeted Immune Cells to Metastatic Brain Tumors</td>
<td>Ryan Alkins, Alison Burgess, Milan Ganguly, Giulio Francia, Robert Kerbel, Winfried S. Wels, and Kullervo Hynynen</td>
<td>Precise: Noninvasive MR-guided focused ultrasound allows targeted natural killer cells to circumvent the blood-brain barrier and treat HER2-amplified breast metastasis in the brain.</td>
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<td>1900</td>
<td>Caveolin-1–LRP6 Signaling Module Stimulates Aerobic Glycolysis in Prostate Cancer</td>
<td>Salahaldin A. Tahir, Guang Yang, Alexei Goltssov, Ki-Duk Song, Chengzhen Ren, Jianxiang Wang, Wenjun Chang, and Timothy C. Thompson</td>
<td>Precise: This study offers mechanistic insights into how aerobic glycolysis is increased in prostate cancer, possibly revealing critical targets for effective antimetabolic therapy in this setting.</td>
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Mixed Lineage Kinase MLK4 Is Activated in Colorectal Cancers Where It Synergistically Cooperates with Activated RAS Signaling in Driving Tumorigenesis
Miriam Martini, Mariangela Russo, Simona Lamba, Elisa Vitelli, Emily Hannah Crowley, Francesco Sassi, Davide Romanelli, Milo Frattini, Antonio Marchetti, and Alberto Bardelli
 précis: Findings support the development of small molecule inhibitors of the kinase MLK4 to treat the significant number of KRAS-mutant colorectal cancers that arise in humans.

A Novel Inhibitor of STAT3 Homodimerization Selectively Suppresses STAT3 Activity and Malignant Transformation
Xiaolei Zhang, Ying Sun, Roberta Pireddu, Hua Yang, Muradi K. Uslan, Harshani R. Lawrence, Wayne C. Guida, Nicholas J. Lawrence, and Said M. Sebti
 précis: STAT3 provides critical support in cancer cells and the immune microenvironment in tumors, but bioactive small molecule inhibitors that offer tractable qualities for clinical translation have been elusive.

Alkaline Phosphatase ALPPL-2 Is a Novel Pancreatic Carcinoma-Associated Protein
Pooja Dua, Hye Suk Kang, Seung-Mo Hong, Ming-Sound Tsao, Soyoun Kim, and Dong-ki Lee
 précis: An aptamer selection strategy identifies an enzyme that may be useful for blood-based detection of pancreatic cancer.

mTOR Complex 2 Is Involved in Regulation of Cbl-Dependent c-FLIP Degradation and Sensitivity of TRAIL-Induced Apoptosis
Liqun Zhao, Ping Yue, Fadlo R. Khuri, and Shi-Yong Sun
 précis: Findings show how mTORC2 stabilizes the FLIP apoptotic regulators, thereby connecting mTORC2 signaling to death receptor-mediated apoptosis.

Phenotypic Profiling of DPYD Variations Relevant to 5-Fluorouracil Sensitivity Using Real-time Cellular Analysis and In Vitro Measurement of Enzyme Activity
Steven M. Offer, Natalie J. Weyner, Croix Fossum, Kangsheng Wang, and Robert B. Diasio
 précis: An understanding of the contribution of DPYD alleles to 5-FU toxicity will facilitate the generation of clinically relevant predictive tests and promote the individualization of treatment based on genotype.

Involvement of Lyn and the Atypical Kinase SgK269/PEAK1 in a Basal Breast Cancer Signaling Pathway
 précis: This study addresses a rationale to target basal breast cancers, also known as triple negative breast cancers, which present a major clinical challenge due to their aggressive nature and lack of targeted treatments.

FOX2C Expression Links Epithelial–Mesenchymal Transition and Stem Cell Properties in Breast Cancer
Brett G. Hollier, Agata A. Tinnirello, Steven J. Werden, Kurt W. Evans, Joseph H. Taube, Tapasree Roy Sarkar, Nathalie Sphyris, Maryam Shariati, Sreedevi V. Kumar, Venkata L. Battula, Jason I. Herschkowitz, Rudy Guerra, Jeffrey T. Chang, Naoyuki Miura, Jeffrey M. Rosen, and Sendural A. Mani
 précis: Findings of this study suggest a rational new target for anti-EMT therapy of cancer stem cells, perhaps relevant to many types of malignancy.

Characterization of a Novel PERK Kinase Inhibitor with Antitumor and Antiangiogenic Activity
Charity Atkins, Qi Liu, Elisabeth Minthorn, Shu-Yun Zhang, David J. Figueroa, Katherine Moss, Thomas B. Stanley, Brent Sanders, Aaron Goetz, Nathan Gaul, Anthony E. Choudhury, Hasan Alsaid, Beat M. Jucker, Jeffrey M. Axten, and Rakesh Kumar
 précis: Inhibition of PERK kinase, which controls the unfolded protein response (UPR), a near universally elevated process in cancer cells, was also found unexpectedly to affect amino acid metabolism, blood vessel density, and vascular perfusion in tumors.

Genetic Amplification of the NOTCH Modulator LNX2 Upregulates the WNT/β-Catenin Pathway in Colorectal Cancer
Jordi Camps, Jason J. Pitt, Georg Emmons, Amanda B. Hummon, Chanelle M. Case, Marian Grade, Tamara L. Jones, Quang T. Nguyen, B. Michael Ghdadimi, Tim Beisbarth, Michael J. Dillilippantionio, Natasha J. Caplen, and Thomas Ried
 précis: Notch and Wnt signaling pathways are upregulated by overexpression of a ligand for the endocytic adaptor protein Numbb, a Notch inhibitory protein, coordinately stimulating both of these critical oncogenic pathways in colorectal cancer.
ABOUT THE COVER

Inactivation of the tumor suppressor p53 frequently occurs in tumors and tumor-associated stromal cells. This study shows that p53 dysfunction in tumor-associated stroma of B16F1 melanoma favors tumor establishment and progression by promoting an inflammatory microenvironment. Using immunofluorescence, it was found that lymphoid-like fibroblastic reticular cells, which express ER-TR7 (green), GP38 (red), and α-SMA (blue), were markedly expanded in the tumor microenvironment lacking functional p53. The expansion of this specialized stromal network was associated with augmented myeloid derived suppressor cells and angiogenesis. For details, see the article by Guo and colleagues on page 1668.